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Research Article

A Cross-Sectional Comparative Study of Methadone Dosage in Adults with and Without ADHD Symptoms under Maintenance Therapy

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Abstract

Background: ADHD often continues into adulthood and can be difficult to manage effectively. For opioid use disorder, methadone is regarded as the first-line treatment option. This study aims to compare methadone dosage in patients undergoing maintenance therapy, with and without symptoms of ADHD.

Methods: This cross-sectional study involved 230 patients receiving methadone maintenance therapy at Shahid Zakarian Health Center in Babol during 2023-2024. ADHD diagnoses were established using the ASRS-v1.1 questionnaire. Data were analyzed using SPSS software, with significance level under 0.05. Specifically, linear regression models were used to explore associations between methadone dosage and ADHD symptoms.

Results: Out of 230 patients, 80 (34.79%) exhibited symptoms of ADHD. The average age of these patients was 43.91 years, with the majority being under 30 years old and unmarried. There was no statistically significant difference in methadone dosage between patients with ADHD symptoms (68.38 mg) and those without (69.73 mg) (P = 0.771). There was a weak, non-significant correlation between ASRS scores and methadone dosage (r = -0.063, P = 0.344). Additionally, none of the demographic variables such as gender (with B Coefficient = 5.85 for females), marital status (B Coefficient = 8.37 for married individuals), or education level (B Coefficient = 2.59 for those with lower education) were significant predictors of methadone dosage.

Conclusion: Methadone dosage in patients with ADHD symptoms did not significantly differ from those without symptoms and was not influenced by demographic variables. However, early screening and individualized dosage adjustments for patients with ADHD, particularly men, married individuals, and those with lower education levels, are recommended.

Keywords: Attention Deficit Disorder with Hyperactivity, Methadone, Attention Deficit Disorder, ADHD, Maintenance.

Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is the most prevalent neurodevelopmental disorder, with a substantial impact on quality of life. ADHD affects around 11% of children and adolescents and 4.4% of adults (1). In adults, ADHD is a psychiatric disorder that often starts in childhood. It is characterized by persistent patterns of inattention, hyperactivity, and impulsive behavior (2). Impulsivity, in this context, refers to actions performed without prior thought or assessment of potential positive or negative outcomes. While ADHD is commonly considered a childhood disorder that can improve with treatment, numerous studies indicate that it persists into adulthood and is challenging to treat (3, 4). A significant issue for individuals with ADHD is its high comorbidity with substance use, with co-occurrence rates of 14-23%, and undiagnosed or untreated ADHD reported at 56% (5). Individuals with ADHD have a twofold higher likelihood of engaging in substance use, influenced by factors such as impaired judgment, impulsivity, and a tendency toward risk-taking. For many, substance use acts as a coping mechanism to manage their symptoms (6, 7).

Substance abuse, one of the most pressing social issues, causes significant harm to both society and families (8-10). According to the 2022 United Nations Office on Drugs and Crime report, approximately 284 million people aged 15 to 64 engage in illegal drug use, reflecting a 26% increase compared to 2021. Of these, around 16 million are addicted to opiates (11). Iran, due to its geographical and cultural circumstances, faces a heightened risk from this phenomenon. According to the Iranian Anti-Narcotics Headquarters, 2.5% of the population are drug users (12). One of the effective pharmacological treatments for managing substance dependence is methadone. This medication acts as a maintenance therapy by alleviating withdrawal symptoms and reducing pain (13). Methadone maintenance therapy reduces opioid overuse, lowers mortality rates, and decreases illegal activities. As a result, it is acknowledged as the primary, evidence-supported treatment for opioid use disorder (14-16). However, medications used to treat substance abuse tend to be less effective in patients with comorbid psychiatric disorders, as their symptoms often complicate treatment. Numerous studies have indicated that individuals with both psychiatric disorders and addiction require higher doses of methadone and longer treatment periods compared to those suffering from addiction alone (17, 18). A 2012 study by Parvaresh et al. also found that co-occurring psychiatric disorders in substance use patients necessitate higher methadone doses for effective treatment (17). Levin et al. found that individuals with ADHD in methadone maintenance therapy may require different treatment approaches compared to those without ADHD, yet the exact differences in methadone dosage have not been fully explored in large cohorts (19). Furthermore, Brooks et al. highlighted the cognitive challenges faced by methadone-maintained patients with ADHD, but their research did not specifically compare methadone dosages between ADHD-positive and ADHD-negative groups (20).

Given that ADHD persists into adulthood and is challrooenging to treat, and considering that individuals with ADHD symptoms are more prone to substance abuse, no previous study has compared methadone dosage in patients with and without adult ADHD symptoms, either in Iran or globally. Therefore, this study aims to compare the methadone dosage in patients undergoing maintenance therapy with and without symptoms of adult ADHD.

Methods

This cross-sectional study was conducted between 2023 and 2024 on all patients undergoing methadone maintenance therapy. Participants included individuals aged 18-60 who had been on methadone maintenance therapy for at least six months and did not suffer from cognitive disorders, psychosis, or suicidal thoughts (based on their medical history and self-reporting). Sampling was carried out after obtaining written approval from the University Research Department and permission from the director of Shahid Zakarian Urban Health Center in Babol. In line with best practices for observational research, this study adhered to the STROBE guidelines for reporting.

The sample size for this study was determined using the methodology from Parvaresh et al. (17). The calculation applied the following parameters: a standard deviation of 43, a margin of error (d) of 15, an alpha level (α) of 5%, and a beta level (β) of 2%. Allowing for a 10% dropout rate, 70 samples were calculated for each group. To account for possible non-cooperation among participants and to enable a thorough analysis of the study variables, the study included a total of 230 eligible participants. Since the total number of patients under methadone maintenance therapy at Shahid Zakarian Center was 119, two private addiction treatment centers were also included in the sampling process, with one center treating 90 patients and the other treating 80.

Questionnaires were distributed among 242 patients undergoing methadone maintenance therapy, of whom 12 were excluded due to incomplete responses, leaving 230 participants in the study. Convenience sampling was employed, and informed written consent was obtained from all participants after explaining the study's purpose and methods in detail. The questionnaire included questions about patients' history of psychotic or cognitive disorders and suicidal thoughts, and their medical records were reviewed for such histories. All participants completed demographic questionnaires and the Adult ADHD Self-Report Scale (ASRS), which were administered under the supervision of the study’s medical student and collaborating psychologist.

The Adult ADHD Self-Report Scale (ASRS-v.1.1), as reported by Kessler et al. (21), consists of two dimensions: inattention (9 questions) and hyperactivity/impulsivity (9 questions), divided into Parts A and B. Responses were scored on a 5-point Likert scale, ranging from "never" (1 point) to "almost always" (5 points). Research by Mokhtari et al. (22) in Iran reported the questionnaire’s reliability at 87% as measured by Cronbach's alpha. Additionally, with a diagnostic cut-off score of 50 for adult ADHD, the questionnaire demonstrated a sensitivity of 70% and a specificity of 99%.

The collected data were processed in SPSS software version 22, where they underwent both quantitative and qualitative analysis. For descriptive statistics, the mean and standard deviation were calculated for numerical variables, while frequencies and percentages were determined for categorical variables. Inferential analysis included the chi-square test to evaluate the association between categorical variables and ADHD symptoms. The independent t-test was used to compare the average methadone dose between groups with and without ADHD symptoms, along with other binary categorical variables. Additionally, the Pearson correlation test to examine the relationship between ADHD symptoms (as measured by ASRS scores) and methadone dosage. Finally, univariate and multivariate linear regression analyses explored associations between methadone dosage, ADHD symptoms, and various demographic factors, with regression coefficients reported as effect sizes. Results with a p-value below 0.05 were considered statistically significant.

Results

Out of the 230 eligible patients, 78.7% (181 individuals) were male, and 56.5% (130 individuals) were between 30 and 50 years old. Additionally, 82.2% (189 individuals) were married, 65.7% (151 individuals) were employed, and 73.1% (168 individuals) had an education level below a high school diploma. Among all participants, 65.21% (150 individuals) had no ADHD symptoms, while 34.79% (80 individuals) exhibited ADHD symptoms. The analysis of the relationship between demographic variables and the presence or absence of ADHD symptoms revealed a significant association between age and ADHD symptoms (P = 0.004). Additionally, a significant relationship was observed between marital status and ADHD symptoms (P = 0.001), with single individuals showing a higher prevalence of ADHD symptoms (Table 1).

Table 1: Demographic Characteristics and Their Association with ADHD Symptoms in Methadone Maintenance Therapy Patients

Variable*		**F (%) Total = (230)**	**With ADHD Symptoms (n = 80)**	**Without ADHD Symptoms (n = 150)**	**P-value****
Gender	Male	181 (78.7)	60 (33.1)	121 (66.9)	0.317
	Female	49 (21.3)	20 (40.8)	29 (59.2)	
Age (years)	Under 30	12 (5.2)	8 (66.7)	4 (33.3)	0.004
	30 - 50	130 (56.5)	51 (39.2)	79 (60.7)	
	Over 50	88 (38.3)	21 (23.9)	67 (76.1)	
Marital Status	Single	41 (17.8)	24 (58.5)	17 (41.5)	0.001
	Married	189 (82.2)	56 (29.6)	133 (70.4)	
Employment	Employed	151 (65.7)	46 (30.5)	105 (69.5)	0.057
	Unemployed	79 (34.3)	34 (43.0)	45 (57.0)	
Education Level	Illiterate	38 (16.5)	12 (31.6)	26 (68.4)	0.205
	Elementary	68 (29.6)	61 (33.9)	119 (66.1)	
	Middle School	62 (27.0)			
	High School	50 (21.7)			
	University	12 (5.2)	7 (58.3)	5 (41.7)	

F; frequency,

* Data are displayed as numbers (%) throughout the table.

**The Pearson Chi-square test was applied, with a significance threshold set at P<0.05.

The mean age and standard deviation for patients with ADHD symptoms were 43.91 ± 11.25 years, while for those without symptoms, it was 49.29 ± 13.36 years. The mean methadone dosage for patients with ADHD symptoms was 68.38 ± 35.34 mg, and for those without symptoms, it was 69.73 ± 32.80 mg. The average difference in methadone dosage between the groups was 1.35 mg (MD = 1.35, 95% CI: -7.83 to 10.55), with slightly higher doses observed in patients without ADHD symptoms. However, this difference did not reach statistical significance (P = 0.771). Furthermore, the correlation analysis between ASRS scores and methadone dosage indicated a very weak and non-significant relationship between the two variables (P = 0.344, r = -0.063) (Figure 1).

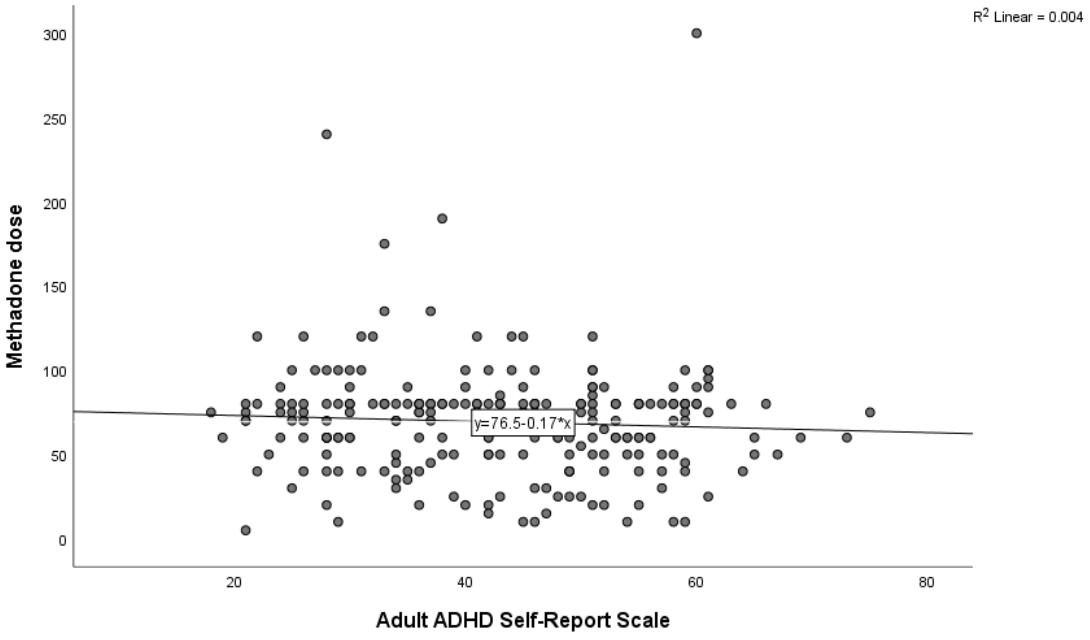

Figure 1 Scatter plot illustrating the correlation between ADHD scores and methadone dosage

In the analysis of the relationship between methadone dosage, ADHD, and other demographic variables using univariate and multivariate linear regression, the results indicated that with each one-point increase in the ASRS score, the methadone dosage decreased by 0.17 units on average, respectively, though this relationship was not statistically significant. Additionally, although no significant associations were found between methadone dosage and ADHD based on other demographic variables, some coefficients, such as marital status (B Coefficient > 8 in both regressions) and gender (OR > 5 in both regressions), were noteworthy (Table 2).

Table 2: Association between ADHD Scores, Methadone Dosage, and Other Variables Based on Univariate and Multivariate Linear Regression Analyses

Variable*	**ULR**				**MLR**			
	B Coefficient	95 % CI	p-value**	t value	B Coefficient	95 % CI	p-value**	t value
ASRS Score	-0.17	-0.52 to 0.18	0.344	-0.947	-0.11	-0.47 to 0.25	0.532	-0.625
Age (years)	0.06	-0.28 to 0.39	0.735	0.338	-0.04	-0.43 to 0.34	0.822	-0.225
Gender (Male than Female)	-5.41	-16.08 to 5.26	0.319	-1.0	-5.85	-19.54 to 7.84	0.401	-0.842
Marital Status (Single than Married)	9.48	-1.88 to 20.86	0.102	1.643	8.37	-3.60 to 20.34	0.170	1.378
Education Level (Illiterate and Lower diploma than Diploma/University)	-2.64	-12.31 to 7.03	0.591	-0.537	-2.59	-13.84 to 8.65	0.650	-0.455
Employment (Employed than Unemployed)	-3.02	-12.23 to 6.19	0.519	-0.646	0.63	-11.53 to 12.79	0.919	0.102

CI; Confidence Interval, ULR; Univariate linear regression, MLR; Multivariate linear regression, ASRS; Adult ADHD Self-Report Scale

*Dependent variable: Methadone dosage; Independents: ASRS Score, Age (years), Gender (Female considered as reference), Marital Status (Married considered as reference), Education Level (Diploma/University considered as reference), and Employment (Unemployed considered as reference).

** A P-value below 0.05 is regarded as statistically significant.

Discussion

In this study, 230 patients undergoing methadone maintenance therapy were assessed for ADHD status. Among them, 80 patients were identified as having ADHD symptoms based on the ASRS-v.1.1 questionnaire. The analysis showed that methadone dosage did not differ significantly between patients with ADHD symptoms and those without. While men, married individuals, and employed patients tended to receive higher methadone doses, no statistically significant association was found between these demographic factors and methadone dosage in the two groups. Additionally, a weak and non-significant correlation was observed between methadone dosage and ASRS scores.

Methadone acts as a secondary treatment option for opioid dependence, primarily used for pain management. Its cost-effectiveness compared to other long-acting opioids makes it particularly suitable for patients with financial challenges (23). Methadone, a synthetic opioid, relieves pain by inhibiting serotonin and norepinephrine reuptake in the central nervous system, blocking NMDA receptors, and stimulating opioid receptors in the brain, primarily the mu-opioid receptor. This dual action enhances its effectiveness in managing pain, relieving withdrawal symptoms, and reducing cravings in opioid-dependent individuals. Additionally, methadone modulates the transmission of pain signals, reducing hyperalgesia and opioid tolerance, while also indirectly influencing dopamine release through its action on opioid receptors, affecting the dopaminergic system (23, 24). Due to the significant variability in methadone's pharmacokinetics, predicting the precise relationship between dosage, plasma levels, and its pharmacological effects is challenging. Therefore, a solid understanding of methadone’s pharmacology is critical for ensuring safe usage. This study aims to assess the average methadone dose in patients who exhibit ADHD symptoms.

The high prevalence of adult ADHD among individuals undergoing methadone maintenance treatment is well-documented (25). However, there is a scarcity of studies that directly compare methadone dosages between those with ADHD and those without. A study by Parvaresh et al. (17) found that out of 154 patients receiving methadone maintenance therapy, 4 had adult ADHD symptoms, with an average maintenance dose of 70 mg similar to the dosage reported for ADHD patients in this study. Levin et al. (19) conducted a study on 33 ADHD patients undergoing methadone treatment and found that their average maintenance dose was 81 ± 37 mg, which is higher than the mean methadone dosage for ADHD patients in this study. In a 2008 study conducted by Brooks et

al. on a cohort of 79 individuals receiving methadone maintenance treatment, it was observed that 18 patients showed symptoms of ADHD (20). The average daily methadone dose for this group was 64.1 ± 25.5 mg, which was lower than the dose observed in the control group. These results align with the findings from this study. In contrast, Coppola et al. (26) reported findings from a sample of 104 patients receiving methadone maintenance therapy, where 14 showed symptoms of ADHD. In this group, the average methadone dosage was higher than that of the control group. Similarly, a study by Kolpe et al. (27) identified a connection between ADHD symptoms and poorer outcomes in methadone treatment. This association is particularly notable given the common lack of ADHD screening among patients with opioid dependence.

It is important to note that various studies have reported different methadone maintenance doses, typically ranging between 60 to 90 mg (17, 19, 20). In some studies, the maintenance dose was higher in ADHD patients (26), while in others it was lower (17, 20). However, the key finding in nearly all studies is the lack of a significant relationship between methadone dosage and ADHD. The variations in methadone dosage for ADHD patients across different studies could be attributed to factors such as clinic policies for addiction treatment, the type of accompanying opioid use, the timing of substance use onset, and even the duration of ADHD. Additionally, it should be noted that the method of ADHD diagnosis whether through self-reported symptoms or standardized tools differs across studies, potentially influencing the diagnosis and subsequent findings in these patients. Notably, this study is the first to report that methadone dosage decreases as ASRS scores increase. These findings indicate that patients who are more likely to exhibit ADHD symptoms require close monitoring of their methadone dosage. This is due to an increased risk of overdose associated with methadone use in this population. In response to this issue, the U.S. Food and Drug Administration (FDA) issued a public health advisory. This advisory emphasizes the importance of precise methadone administration, especially in light of the rising number of overdose-related deaths among individuals using methadone for pain management. They noted that some cases of unintentional overdose were linked to a lack of physician awareness about methadone's pharmacokinetics and potential side effects (28).

One limitation of this study is that it was conducted in a single center, making it difficult to generalize the findings to the broader population. Also, the use of non-random sampling could affect the generalizability of the results, as the sample may not be fully representative of the broader population undergoing methadone maintenance therapy. To improve generalizability, future studies should include larger sample sizes and be conducted across multiple centers within the province. Another limitation is the lack of data on the

patients' current medications, age at first substance use, duration of methadone treatment, and the type of opioid used prior to methadone initiation. These variables could act as confounding factors, potentially influencing the study results. Also, the study did not assess other psychological criteria in the diagnosis of ADHD, which could act as potential confounders. Additionally, it is important to note that different studies have used various questionnaires for ADHD diagnosis and screening, which could explain the variation in reported ADHD prevalence among patients undergoing methadone maintenance therapy.

Conclusions

In summary, this study did not observe any notable difference in methadone maintenance doses between individuals with ADHD and those without. Additionally, univariate and multivariate regression analyses indicated that none of the demographic variables could predict ADHD in patients undergoing methadone maintenance therapy. These findings can assist addiction specialists and physicians in adjusting methadone dosages and facilitating early identification of ADHD patients. Moreover, this data may contribute to improving social outcomes through timely diagnosis and the implementation of appropriate treatment policies for patients in need.

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Ethics approval and consent to participate

The study's research proposal received approval from the Research Ethics Committee at Babol University of Medical Sciences, under the reference code IR.MUBABOL.HRI.REC.1402.250. Not revealing the secrets and private issues of the patients, keeping the information obtained from them confidential and announcing the results of the research without mentioning names and personal details are considered.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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None.

Author Contribution:

A.M. acted as the primary author and guarantor, contributing to data interpretation and manuscript revision. S.B.K., M.B., and H.G.A. were responsible for study design and led both the drafting and revision processes for the manuscript. All authors reviewed and approved the final submitted version. Each author actively participated in the manuscript preparation, reviewed its contents, and provided approval for submission.

Conflict of interest

The authors declare that they have no competing interests.

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